SYNOPSIS

ON THE TOPIC ENTITLED

DEVELOPMENT AND CHARACTERIZATION OF ANTIBACTERIAL NANOPARTICULATE DRUG DELIVERY SYSTEMS FOR PROSTATITIS INFECTIONS

TO BE SUBMITTED TO

RESEARCH AND RECOGNITION COMMITTEE

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BY

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Development and Characterization of Antibacterial Nanoparticulate Drug Delivery Systems for Prostatitis Infections

Abstract of proposed work plan/ problem:

Prostatitis is swelling of the prostate gland. Prostate tissue becomes inflamed. This problem can be caused by an infection with bacteria. Acute prostatitis starts quickly and chronic prostatitis lasts for 3 months or more. Any bacteria that can cause a urinary tract infection can cause acute bacterial prostatitis. Symptoms can start quickly, and can include Chills, Fever, Flushing of the skin Symptoms of chronic prostatitis are similar, but not as severe. They often begin more slowly. Some people have no symptoms between episodes of prostatitis. Prostatitis may affect the results of the prostate-specific antigen (PSA), a blood test to screen for prostate cancer. An antibiotic would be selected to formulate polymeric nanoparticles Drug Delivery System. Preformulation studies, characterization of drug and polymeric material and other excipients by analytical methods (viz. FTIR, HPLC, DSC-TGA, XRD, and SEM) followed by formulation of nanoparticulate dosage forms. *In-vitro* release studies on formulations. Selected formulation would be subjected to *in-vitro* antibacterial studies against causative agent of prostatitis and *In-vivo* bioavailability studies, effects of formulation on prostatitis mouse model or *In-vitro* prostatitis model studies and six months stability studies as per ICH guidelines.

Key Words: Prostatitis, Antibiotic, Nanoparticles, Antibacterial Activity, *In-Vivo* Toxicity, Stability Studies.

1. Introduction:

Mainly because of patient convenience and acceptability oral route is the most convenient route of administration and oral drug delivery is the most preferable and desirable method of administering therapeutic agents for systemic effects. Traditional methods of formulation are still being employed which provide clinically effective therapy and safety to the patient by maintaining the required balance between the pharmacodynamic and pharmacokinetic profiles. In order to overcome the limitations of conventional therapy, wide variety of oral drug delivery systems have been developed in recent years which provides sustained release dosing and are able to maintain steady drug plasma levels for extended periods of time with reduced drug related side effects.

Prostatitis is the most common urological diagnosis in men <50 years of age and is the third most common diagnosis among those 50 years of age. Approximately 10% of men have chronic prostatitis-like symptoms; of these men, 60% have sought medical help. The lifetime probability of a man receiving a diagnosis of prostatitis is 125%, and prostatitis accounts for 25% of men's office visits for genitourinary complaints. Reported rates of prostatitis are similar in North America, Europe, and Asia. In addition to discomfort, prostatitis syndromes are responsible for substantial physical and emotional distress and financial costs.

The prostate gland has several natural defenses against infection, including the production of antibacterial substances and mechanical flushing of the prostatic urethra by voiding and ejaculation. However, poor drainage of secretions from peripheral ducts or reflux of urine into prostatic tissue may lead to inflammation, fibrosis, or stones. Most bacterial prostatitis probably follows a urinary tract infection (UTI), especially with uropathogens that demonstrate special virulence factors Risk factors for developing prostate infection include urinary tract instrumentation, having a urethral stricture, or urethritis (usually due to sexually transmitted pathogens).

ABP, which accounts for <1% of cases of prostatitis, is likely caused by infected urine ascending the urethra to intra prostatic ducts. The 10% of cases that follow genitourinary instrumentation generally occur in older patients, have a higher risk of recurrence or prostatic abscess, and are more often caused by non–*Escherichia coli* species. Despite antibiotic prophylaxis,2% of men

develop ABP after trans rectal prostate biopsy, especially after repeat procedures . CBP complicates a minority of cases of ABP and often occurs without a previous acute infection. The formation of either bacterial biofilm or prostatic calculi favors chronic, treatment-resistant infection.[1-3]

Sustained-release dosage forms reduce side effects and increases safety and patient compliance by reducing the frequency of dosing[1]. Drug release-retarding materials play an important role in such systems. Various materials are thus investigated for sustaining the release from the drug-loaded matrices. Some of them such as a chitosan, sodium alginate and xanthan gum have been thoroughly reviewed. Of the various approaches to formulate sustained release matrices, one method is to incorporate drug within the release retarding polymer. Most commonly used polymers for such operations are cellulose ether derivatives, including Hydroxypropyl methylcellulose (HPMC).[4]

Stability testing of pharmaceutical products is a complex set of procedures involving considerable cost, time consumption and scientific expertise in order to build in quality, efficacy and safety in a drug formulation. Scientific and commercial success of a pharmaceutical product can only be ensured with the understanding of the drug development process and the myriad tasks and milestones that are vital to a comprehensive development plan. The most important steps during the developmental stages include pharmaceutical analysis and stability studies that are required to determine and assure the identity, potency and purity of ingredients, as well as those of the formulated products. Stability of a pharmaceutical product may be defined as the capability of a particular formulation in a specific container/closure system to remain within its physical, chemical, microbiological, toxicological, protective and informational specifications.

In other words, it is the extent to which a product retains, within the specified limits, throughout its period of storage and use, the same properties and characteristics possessed at the time of its packaging. Stability testing thus evaluates the effect of environmental factors on the quality of the a drug substance or a formulated product which is utilized for prediction of its shelf life, determine proper storage conditions and suggest labeling instructions. Moreover, the data generated during the stability testing is an important requirement for regulatory approval of any drug or formulation.[8-9]

2.0 Review of Literature and Development in the subject (Previous work done in the relevant area):

Relevant literatures were identified by performing a PubMed, DOAJ, Science Direct search were critically reviewed, and data interpreted.

1. Li Chong et al. demonstrated Considering that some antibacterial agents can identify the outer structure of pathogens like cell wall and/or cell membrane, they explored a self-enhanced targeted delivery strategy by which a small amount of the antibiotic molecules were modified on the surface of carriers as targeting ligands of certain bacteria while more antibiotic molecules were loaded inside the carriers , and thus has the potential to improve the drug concentration at the infection site, enhance efficacy and reduce potential toxicity.[15]

2. D. Krishnarajan et al. developed matrix tablets of levofloxacin for sustained release. Xanthan gum, guar gum, karaya gum used as natural polymers and study the effect of various formulation factors such as polymer proportion and effect of filler type on the in vitro release of the drug. Levofloxacin Matrix tablets were prepared by direct compression technique with average weight of drug of 250 mg. The prepared tablets were evaluated for weight variation, friability, hardness, thickness and in vitro dissolution studies. All the granules of formulations showed compliance with pharmacopoeial standards. From the *In vitro* dissolution studies it is clear that by increasing the amount of drug release is decreased as the concentration of polymer increased, drug release was found to be retarded.[2]

3. K. Ramesh et.al ; studied on the design of sustained release matrix tablet of a widely used drug levofloxacin hemi hydrate. Matrix tablets of levofloxacin hemihydrate were prepared by employing both hydrophilic and hydrophobic polymers (HPMC, Ethyl cellulose, Compritol and almond gum). The tablets prepared by employing the relatively unexplored hydrophilic almond gum showed acceptable pharmaceutical properties. Matrix tablets prepared with polymers other than almond gum though gave a slow release. It was observed that more than 90% of drug was released by 8 hrs. A slow drug release of about 90% extended up to 12 hrs was obtained with tablets prepared by employing almond gum. Studies are also made on the influence of changing the microenvironment of the matrix on the release profile of the drug. Inclusion of citric acid in the formulation favored the release of the drug from the matrix tablets.[4]

3.0 Objectives of Research/ Proposed Hypothesis:

The objective of the proposed work is

- To perform compatibility studies on selected drug, polymer, and excipients
- To select recent two antimicrobial drug for formulation of nanoparticles by Freezdrying, Spray drying, Sonication, Emulsification, Solvent evaporation.
- .To evaluates the percent drug loading and percent entrapment efficiency.
- To characterized nanoparticles.
- To formulate suitable dosage form of formed nanoparticles
- To analyze the formulation by different analytical methods.
- To study *In vitro* drug release
- To estimate kinetics of selected dosage forms.
- To perform stability study as per ICH guidelines.
- To determine dosage form efficacy against causative microorganism of prostatitis.
- To perform *In vivo* studies on selected formulation.
- Effects of formulation on mouse model of prostatitis or *In vitro* prostatitis model.
- *In vivo* bioavailability studies on animals.

4.0 Methodology to be adopted:

4.1Preformulation studies

Compatibility studies.
Differential scanning calorimetry (DSC)
Solubility study of Drug.

4.2 Determination of maximum wavelength absorption of Drug and preparation of calibration curve of Drug by using UV- spectrophotometer.

4.3 Assay for Drug - polymer-adsorbent complex, prepared in three different ratios.

4.4 Formulation of Nanoparticles by suitable methods.

4.5 Evaluation and Characterization of formed nanoparticles.

4.6 Formulation of suitable dosage form containing nanoparticles.

4.7 *In vitro* drug release studies of formulations.

4.8 Analysis of selected formulation by FT-IR, DSC and XRD technique.

4.9 Stability study on selected formulation.

4.10 Kinetic study on selected formulation.

4.11 Effects of formulation on mouse model of prostatitis or *In vitro* prostatitis model.

4.12 *In vitro* antibacterial studies against causative agent of prostatitis

4.13 *In vivo* bioavailability studies on animals.

5.0 Importance of study/ Society application:

5.1 International status

Almost 9% of Canadian men experience some prostatitis symptoms over the course of a year, in about 6%, the symptoms are a bother, with approximately a third experiencing a remission of symptoms over a year during follow-up. Men with clinically significant prostatitis symptoms account for about 3% of Canadian male outpatient visits and causes significant morbidity and cost. Less than 10% of the patients suffer from acute or chronic bacterial prostatitis, conditions which are well-defined by clinical and microbiologic parameters and usually amenable to antimicrobial therapy. Acute prostatitis is characterized by a severe urinary tract infection (UTI), irritative and obstructive voiding symptoms with generalized urosepsis. Acute prostatitis responds promptly to antimicrobial therapy, and is usually self-limiting. Chronic bacterial prostatitis is usually associated with mild to moderate pelvic pain symptoms and intermittent episodes of acute UTIs.. Most men with "chronic prostatitis" have chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), characterized by pelvic pain (i.e., perineal, suprapubic, testicular, penile) variable urinary symptoms and sexual dysfunction (primarily pain associated with ejaculation).The National Institutes of Health-Chronic Prostatitis Symptom Index (NIH-CPSI) is a reliable means of capturing the symptoms and impact of CP/ CPPS.The etiology of this syndrome is not fully known, the evaluation has been controversial and treatment is, unfortunately, frequently unsuccessful. Focused multimodal therapy appears to be more successful than empiric monotherapy.

5.2 National Status

In India Ayurvedic medicines for prostatitis as alternative treatment are used for chronic prostatitis. Most of the patients suffering from prostatitis not having proper dosage regimen hence condition is untreated .patient specific resistance also developed during treatment.

5.3 Significance of the study

Long-term antimicrobial therapy is curative in about 60% to 80% of patients with acute and chronic symptoms of prostatitis. There is need to develop Novel drug delivery systems as nanoparticles as sustained , controlled ,extended release antimicrobial oral dosage form as

available antibiotics are showing resistance for *E. coli*, the most frequent pathogen, probability is greater than 10% to 20%. Treatment should continue for 2 to 4 weeks to cure the condition.

6.0 Proposed work Plan/ Formulation and Structure of Study:

1. **First Year**

Part I July to December 2016

Literature survey on proposed title

Procurement of drug, polymer and excipients

Pre formulation study

Calibration curve of drug sample

Submission of progress report

Part II January to June 2017

Formulation of nanoparticles by various methods

Evaluation and characterization of nanoparticles.

Formulation of nanoparticulate dosage forms.

In vitro Release studies on all formulations

Submission of progress report

2. **Second Year**

Part I July to December 2017

Calculations and kinetic study based on in-vitro release study.

Evaluation dosage forms

In vitro antimicrobial study of formulation against causative organism of bacterial prostatitis.

Optimization of all parameters so as to fulfill objective to select formulation.

Submission of progress report

Conference presentation

Part II January to June 2018

Stability studies on selected formulation

Analytical studies

Submission of progress report

3. Third Year

Part I July to December 2018

In vivo bioavailability study based on approved protocol

Efficacy of formulation on prostatitis mouse model / In-vitro prostatitis model

Analytical studies

Submission of progress report

Conference presentation

Part II January to June 2019

Review of analytical characterization, kinetic studies, stability studies, bioavailability studies.

Results and discussion followed by Conclusion of the work done

Publication of work

Submission of progress report

Synopsis submission

7.0 References

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